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10/579,029	11/19/2008	Christopher K. Raymond	ROSA127563	2231

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/579,029	RAYMOND, CHRISTOPHER K.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,8-17,19-21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,8-17,19-21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of Applicant's persuasive arguments filed June 16, 2011, the finality of the previous office action has been withdrawn and a new office action has been submitted herein.

Applicant's amendment filed on June 16, 2011 is acknowledged and has been entered. Claims 1 and 21 have been amended. Claims 2, 5, 7, 18, 22, 25-42 have been canceled. Claims 1, 3-4, 6, 8-17, 19-21 and 23-24 are pending.

Claims 1, 3-4, 6, 8-17, 19-21 and 23-24 are discussed in this Office action.

Response to Arguments

Applicant's arguments, see p. 7-13, filed June 16, 2011, with respect to the rejection(s) of claim(s) under 35 U.S.C. 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Jacobsen et al. (US PgPub 20110076675; March 2011; 102(e) date July 23, 2004).

Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL to address new grounds of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-4, 6, 8, 10, 12-21 and 23 are rejected under 35 USC 103(a) as being obvious over Jacobsen et al. (US PgPub 20110076675; March 2011; 102(e) date July 23, 2004).

With regard to claim 1, Jacobsen teaches a method for amplifying a molecule to produce DNA molecules, the method comprising the steps of:

(a) producing a first DNA molecule that is complementary to a target microRNA molecule using primer extension, with an extension primer comprising a first portion having a length from 3 to 17 nucleotides selected to hybridize to a portion of the target molecule and a second portion that

hybridizes to the complement of the universal forward primer (Figure 11(1-2), where an mRNA tagging probe is used as a first extension primer, which comprise between 6-12 nt in length on a microRNA target sequence; paragraph 37; paragraph 92, where the “RT tagging probe” is described as including an anchor sequence "essential for subsequent capture or amplification by PCR" and therefore the second portion hybridizes to a “universal” primer; see also paragraph 149-151, where the method is described in detail); and

(b) amplifying the first DNA molecule to produce amplified DNA molecules using a universal forward primer and a reverse primer, wherein the reverse primer is selected to specifically hybridize to a portion of the first DNA molecule that is complementary to the target microRNA under defined hybridization conditions (Figure 11(1-3) where a second strand is generated, followed by amplification with forward and reverse primers complementary to the anchor sequence of the original tagged probe/primer; see paragraph 149-151, where the method is described in detail).

With regard to claim 3, Jacobsen teaches an embodiment of claim 1 wherein the primer extension uses an extension primer having a length in the range of from 10 to 100 nucleotides (Figure 11(1), where the first extension primer comprises a first portion 6-12 nt in length and a second anchor sequence 15-25 nt in length and therefore the extension primer comprises in full between 21-37 nt in length).

With regard to claim 4, Jacobsen teaches an embodiment of claim 1 wherein the primer extension uses an extension primer having a length in the range of from 20 to 35 nucleotides (Figure 11(1), where the first extension primer comprises a first portion 6-12 nt in length and a

second anchor sequence 15-25 nt in length and therefore the extension primer comprises in full between 21-37 nt in length).

With regard to claim 6, Jacobsen teaches an embodiment of claim 25, wherein the first portion of the extension primer has a length in the range of from 6 to 17 nucleotides (Figure 11(1-2), where an mRNA tagging probe is used as a first extension primer, which comprise between 6-12 nt in length).

With regard to claim 8, Jacobsen teaches an embodiment of claim 1, wherein the second portion has a length of from 18 to 25 nucleotides (Figure 11(1), where the second anchor sequence is 15-25 nt in length).

With regard to claim 10, Jacobsen teaches an embodiment of claim 1 wherein the universal forward primer has a length in the range of from 16 nucleotides to 100 nucleotides (Figure 11(3), where the forward and reverse primers are 20-25 nt in length).

With regard to claim 12, Jacobsen teaches an embodiment of claim 1, wherein the universal forward primer hybridizes to the complement of the second portion of the extension primer (paragraph 92, where the "RT tagging probe" is described as including an anchor sequence "essential for subsequent capture or amplification by PCR" and therefore the second portion hybridizes to a "universal" primer).

With regard to claim 15, Jacobsen teaches an embodiment of claim 1 wherein the reverse primer has a length in the range of from 10 nucleotides to 100 nucleotides (Figure 11(3), where the forward and reverse primers are 20-25 nt in length).

With regard to claim 19 and 21, Jacobsen teaches an embodiment of claim 1 or 21, further comprising the step of measuring the amount of amplified DNA molecules (paragraph 149, step 3, or paragraph 150-151, where the amount of amplified product is detected).

With regard to claim 20, Jacobsen teaches an embodiment of claim 1 wherein amplification is achieved by multiple successive PCR reactions (paragraph 149, step 3, or paragraph 150-151, where the amount of amplified product is detected).

With regard to claim 21, Jacobsen teaches a method for measuring the amount of a target in a sample from a living organism, the method comprising the step of measuring the amount of a target molecule in a multiplicity of different cell types within a living organism, wherein the amount of the target molecule is measured by a method comprising the steps of:
(1) producing a first DNA molecule complementary to the target microRNA molecule in the sample using primer extension with an extension primer comprising a first portion having a length from 3 to 17 nucleotides selected to hybridize to a portion of the target microRNA molecule and a second portion that hybridizes to the complement of the universal forward primer (Figure 11(1-2), where an mRNA tagging probe is used as a first extension primer, which comprise between 6-12 nt in length on a microRNA target sequence; paragraph 37; paragraph 92, where the “RT tagging probe” is described as including an anchor sequence "essential for subsequent capture or amplification by PCR" and therefore the second portion hybridizes to a “universal” primer; see also paragraph 149-151, where the method is described in detail);
(2) amplifying the first DNA molecule to produce amplified DNA molecules using a universal forward and a reverse primer, wherein the reverse primer is selected to specifically hybridize to a portion of the first DNA molecule that is complementary to the target microRNA molecule under

defined hybridization conditions (Figure 11(1-3) where a second strand is generated, followed by amplification with forward and reverse primers complementary to the anchor sequence of the original tagged probe/primer; see paragraph 149-151, where the method is described in detail), wherein a least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule (???); and

(3) measuring the amount of amplified DNA molecule (paragraph 149, step 3, or paragraph 150-151, where the amount of amplified product is detected).

With regard to claim 23, Jacobsen teaches an embodiment of claim 21, wherein the amount of the amplified DNA molecules are measured using fluorescence-based quantitative PCR (Figure 11(3), where the amplified products are measured using fluorescent real-time PCR detection).

Regarding claims 1, 13-14, 16-17 and 21, while Jacobsen teaches LNA modification of the extension primer/probe and/or the detection probe, Jacobsen does not specifically teach that the forward or reverse primers in the embodiment depicted in Figure 11 comprise LNA modifications.

With regard to claim 1 and 21, Jacobsen teaches wherein at least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule (Figure 30, where the forward primer includes an LNA portion prior to amplification; Figure 11, where the extension primer and the detection probe comprise at least one locked nucleic acid molecule).

With regard to claim 13, Jacobsen teaches an embodiment of claim 1, wherein the universal forward primer comprises at least one locked nucleic acid molecule (Figure 30, where

the forward primer includes an LNA portion prior to amplification; Figure 11, where the extension primer and the detection probe comprise at least one locked nucleic acid molecule).

With regard to claim 14, Jacobsen teaches an embodiment of claim 1, wherein the universal forward primer comprises from 1 to 25 locked nucleic acid molecules (Figure 30, where the forward primer includes an LNA portion prior to amplification).

With regard to claim 16, Jacobsen teaches an embodiment of claim 1, wherein the reverse primer comprises at least one locked nucleic acid molecule (Figure 30, where the forward primer includes an LNA portion prior to amplification).

With regard to claim 17, Jacobsen teaches an embodiment of claim 1, wherein the reverse primer comprises from 1 to 25 locked nucleic acid molecules (Figure 30, where the forward primer includes an LNA portion prior to amplification).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Jacobsen to include the LNA modification of the universal forward or reverse primer to arrive at the claimed invention with a reasonable expectation for success. As taught by Jacobsen, "The recognition sequences in the tagging probe set as well as the detection probe are synthesized by substitution of high affinity nucleotide analogues, e.g. LNA, and preferably oxy-LNA, allowing highly sensitive and specific hybridization and ligation to occur at elevated temperatures. By the use of short detection probes of the invention, substituted with high affinity nucleotide analogues, e.g. LNA, LNA diaminopurine and LNA 2-thio-thymidine, short amplicons corresponding to mature miRNAs or siRNAs, including the anchor primer sites from the tagging probe set can be monitored directly in standard real-time quantitative PCR assays" (paragraph 26). Therefore, one of ordinary skill

in the art at the time the invention was made would have been motivated to have adjusted the teachings of Jacobsen to include the LNA modification of the universal forward or reverse primer to arrive at the claimed invention with a reasonable expectation for success.

Claims 9, 11 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen et al. (US PgPub 20110076675; March 2011; 102(e) date July 23, 2004) as applied to claims 1, 3-4, 6, 8, 10, 12-21 and 23 above and further in view of Crollius et al. (Nature Genetics, 2000, 25(2):235-238), Buck et al. (Biotechniques, 1999, 27:528-536) and Spivack et al. (US PgPub 2003/0186288; October 2003).

Jacobsen teaches the limitations of claims 1, 3-4, 6, 8, 10, 12, 15, 18-21 and 23 as recited in the obviousness rejection above. However, Jacobsen does not teach SEQ ID NO:1 or 13.

With regard to claim 9 and 11, Crollius teaches an embodiment of claim 1, wherein the second portion of the extension primer has a nucleic acid sequence comprising the nucleic acid sequence of SEQ ID NO:1 and wherein the universal forward primer consists of the nucleic acid sequence set forth in SEQ ID NO:13 (see alignment below, where AL302487 of Crollius teaches a sequence which comprises SEQ ID NO:1 or 13, and where the sequences are the same, as evidenced by sequence listing).

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Qy          1 CATGATCAGCTGGGCCAAGA 20
              ||||||||||||||||||||
Db        699 CATGATCAGCTGGGCCAAGA 680
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Regarding claim 24, Jacobsen does not teach measurement of the amount of amplified DNA using SYBR green dye.

With regard to claim 24, Spivack teaches an embodiment of claim 21, wherein the amount of the amplified DNA molecules are measured using SYBR green dye (paragraph 95-96, where the amplification products are subjected to agarose or polyacrylamide gel electrophoresis and stained to measure the density of the amplification product, and where the stain includes SYBR green dye).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Jacobsen to use a variety of adaptor/primer tag sequences, including the sequence comprising SEQ ID NO:1 and 13 as taught by Roest in view of Buck. Regarding the universal tag, Spivack teaches, "The present invention relates to 'Universal RT-coupled PCR', a novel PCR strategy that takes advantage of the poly-A tail of processed mRNA, and uses novel 'Universal RT primers' that comprise a unique 5′ tag sequence that does not occur in the genome of the organism being studied (for example the human genome), a poly-T midsection, and a 3′ anchor to avoid slippage. These 5′ tag-enhanced 'Universal RT primers' reliably initiate reverse transcription, and the unique sequence of the 5′ tag is then targeted by the PCR primers (paragraph 53)". While Crollius' sequences puffer fish genomes, it would have been prima facie obvious to one of ordinary skill in the art to have included a variety of adaptor/primer tag sequences. Furthermore, in view of the guidance by Spivack that the unique sequence does not occur in the genome of the organism being studied, choosing a sequence from an unrelated organism like the Tertraodon nigroviridis falls in line with the teachings of Spivack. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Jacobsen to use a variety

of adaptor/primer tag sequences, including the sequence comprising SEQ ID NO:1/13 as taught by Roest in view of Buck.

Regarding Buck, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of puffer fish genome, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical

sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Jacobsen to include both a tag sequence and a portion specific to the target as taught by Spivack to arrive at the claimed invention with a reasonable expectation for success. As taught by Spivack, "The present invention relates to 'Universal RT-coupled PCR', a novel PCR strategy that takes advantage of the poly-A tail of processed mRNA, and uses novel 'Universal RT primers' that comprise a unique 5′ tag sequence that does not occur in the genome of the organism being studied (for example the human genome), a poly-T midsection, and a 3′ anchor to avoid slippage. These 5′ tag-enhanced 'Universal RT primers' reliably initiate reverse transcription, and the unique sequence of the 5′ tag is then targeted by the PCR primers (paragraph 53)". Spivack also teaches "the novel Universal RT primer used for reverse transcription has a 3′ three-base anchor that allows the primer to be positioned on the last 3 bases of the transcript specific sequence and covers all possible combinations of the coding 3′ end of the mRNA transcript (see FIGS. 6 and 7). This allows RNA binding without slippage, and thereby avoids the generation of cDNA's of various sizes" (paragraph 58). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Jacobsen to include both a tag sequence and a portion specific to the target as taught by Spivack to arrive at the claimed invention with a reasonable expectation for success.

Citation of Pertinent Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Tsang et al. (Biotechniques, 2004, 32:682-688) teaches multiplex amplification and genotyping using a universal adaptor sequence (Abstract).

Response to Arguments

Applicant's arguments with respect to claims 1, 3-4, 6, 8-17, 19-21 and 23-24 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM